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Exploring the current status and trends of research on Langerhans Cell Sarcoma: A bibliometric analysis

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ABSTRACT

Langerhans cell sarcoma (LCS) is a highly malignant neoplasm exhibiting aggressive clinical behavior. In this study, we aimed to explore the current status and trends of research on LCS by doing a bibliometric analysis. Data on LCS were retrieved from the Web of Science database and a bibliometric analysis was conducted to measure the impact of publications, authors, organizations, and countries. Different software packages, including BiblioAnalytics, Bibliomaster, MS Excel, MS Access, VOSviewer, Biblioshiny, Power BI, and an online visualization platform were used for analysis and visualization in the present study. A total of 96 publications were included in the present bibliometric analysis. Authors “Lebbe C”, “Lorillon G”, “Mourah S”, and “Tazi A” received the highest number of citations, and the journal “Histopathology” received the highest number of citations. The outstanding organization was the Mayo Clinic in the USA with the highest number of 5 publications and the highest number of 175 citations. Japan and the USA were the outstanding countries that contributed to the research on LCS. Current literature on LCS is minimal, which stresses the need for more research productivity, especially within areas regarding diagnosis and immunohistochemical staining with CD markers for this pathology.

Keywords: langerhans cells, malignant neoplasm, malignant histiocytic disorder, histiocytosis, hemic and lymphatic disease

INTRODUCTION

Langerhans cells are dendritic cells first discovered in 1868 by applying gold chloride to a slide of human epidermal tissue [1]. Langerhans cell sarcoma (LCS) is an abnormal proliferation of Langerhans cells with malignant features particularly those of the skin and other epithelial structures [2, 3]. Development usually occurs at 30-40 years of age; however, the disease may have a wider age of onset and may also present in children [4, 5]. LCS affects multiple organ systems; however, previously published literature has identified the skin, lymph nodes, bone marrow, lungs, spleen, and liver as common sites of involvement [6-8]. Diagnosis of this disease has proved to be difficult since its marked cytologic atypia and pleomorphism is coherent with several other diseases such as malignant melanoma, lymphomas, and other dendritic cell tumors. As a result, a biopsy of this disease would present a clinician with a very broad differential diagnosis [9]. LCS histology reveals distinctive nucleoli with pleomorphism, an increased nuclear-to-cytoplasmic ratio, and a high rate of mitotic activity [6, 10]. The nuclei have also been observed to have prominent nuclear grooves, which are lobulated and consist of prominent eosinophilic nucleoli with a high mitotic rate [11]. It is also important to mention that LCS should not be confused with langerhans cell histiocytosis (LCH), which has a shared cellular origin to that of LCS. Although having identical lineage, LCH and LCS morphology differs from one another with LCH having monoclonal proliferation and having benign course while LCS has been observed to have more malignant features and an unfavorable prognosis [12, 13]. It is widely accepted that LCH, which presents with increased numbers of atypical tumor cells should be considered as LCS and be regarded as a separate entity [2, 14, 15].

Current methods of diagnosis of LCS include the application of immunohistochemical staining. It has been observed that the tumor is particularly selective for S-100 protein, vimentin, as well as CD68, CD1a [13, 16]. The presence of Birbeck granules and langerin (CD207) further helps to reach a diagnosis [17]. The article by Pileri et al. sheds further light into the ultrastructural findings of LCS and its histochemical features [10]. According to the recommendations of the Histiocyte Society, the severity and course of LCS may be classified according to the number of organs that may be affected by this disease at the time of presentation [18, 19].

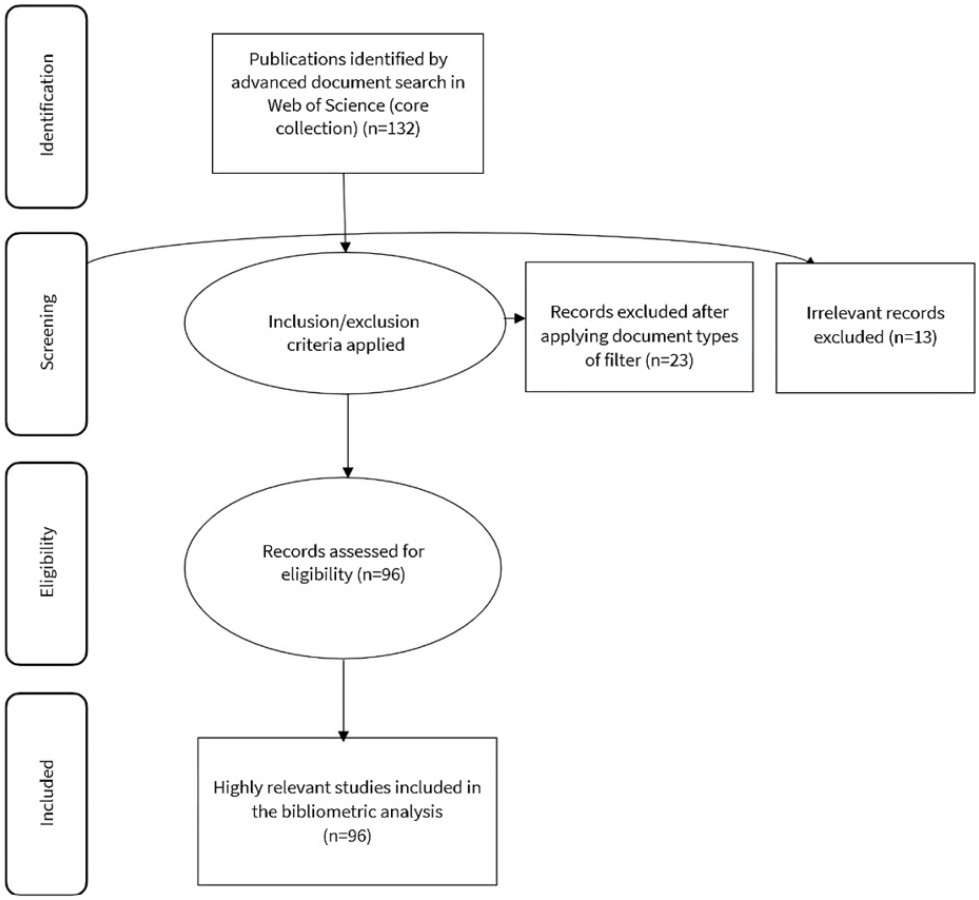


Figure 1. Flowchart depicting the search strategy for inclusion of relevant documents in the bibliometric analysis (Source: Authors' own elaboration, using MS Excel)

The treatment involves chemotherapy coupled with radiation therapy. In cases in which LCS tumor is easily accessible, surgery may be preferred [17]. The study by Lauritzen et al. applied the use of drug therapy vincristine, procarbazine, and mustargen for LCS, however, it is unclear whether this therapy provided any benefit or not [20]. LCS is a rare pathology that is not commonly observed in clinical practice and has been observed to exhibit a poor prognosis; however, regardless of its low incidence, it poses several problems for pathologists and hematologists regarding its therapeutic management and determining whether the disease has become aggressive. Examination of histological features provides no benefit in determining prognosis [21, 22].

Bibliometric analysis is a new frontier of research that uses mathematical reasoning combined with statistical tools to analyze research publications. The purpose of bibliometric research is to shed light on a field, discipline, or subject, and analyze its evolution by mapping the structure and dynamics of disciplines using data and evaluating the performance of authors, institutions, and countries [23]. Monitoring changes in the field aids in interpreting the information available in a specific area and directs public health policy. The number of research publications has drastically increased over the years and continues to rise.

As a result, bibliometric approaches that examine the direction of development in a scientific subject show the dynamics and structure of the field and illustrate the most significant fields of research have become crucial.

The current literature on LCS is limited because of the rarity of the disease, and little attention has been paid to exploring the potential areas of interest regarding this pathology. Hence, we conducted a bibliometric analysis to assess the current level of LCS research and identify new key areas of LCS research that may require more attention to allow new breakthroughs and future implications.

METHODS

Web of Science (WoS) core collection database was used to retrieve and extract data from journal articles on LCS for bibliometric analysis. WoS database, one of the world's leading analytical databases, is a credible source for conducting such studies [24, 25]. All possible keywords related to LCS were carefully reviewed. After a thorough discussion, the medical subject heading (MeSH, National Library of Medicine), "langerhans cell sarcoma" was finalized for data retrieval from WoS database. The following search query was executed on June 20, 2022, for maximum precision and recall: TS=("langerhans cell sarcoma"). This search yielded 132 documents, after removing 23 "meeting abstracts" and 13 irrelevant records, 96 documents were included in the final analysis (**Figure 1**). Software packages, including BiblioAnalytics, Bibliomaster, MS Excel, MS Access, VOSviewer, Biblioshiny, Power BI, and an online visualization platform (https://flourish.studio) were used for analysis and visualization in the present study (**Figure 2**).

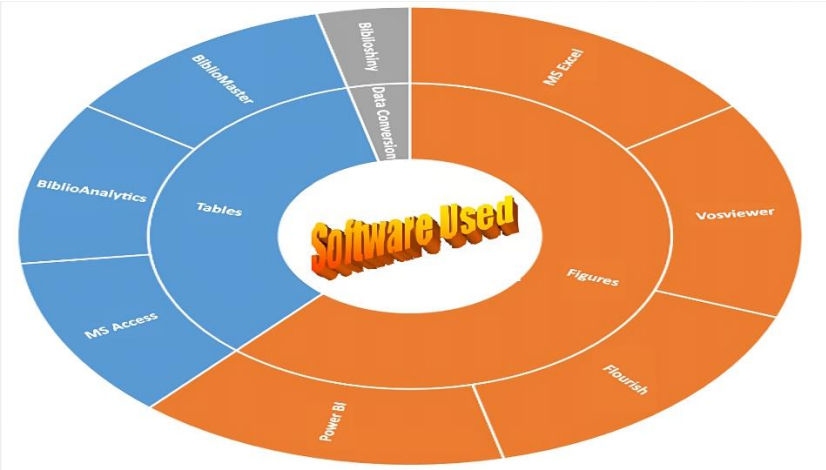


Figure 2. Software/tools used in the process of analyzing the data (Source: Authors' own elaboration, using MS Excel)

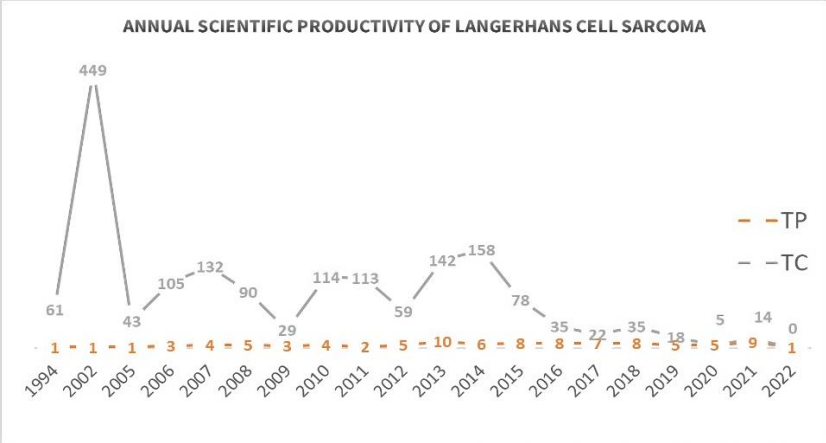


Figure 3. Annual growth in LCS research (Source: Authors' own elaboration, using MS Excel)

Table 1. Document types

Document type	Total publications	Total citations	ATC
Article	58	1,016	17.52
Editorial material	4	13	3.25
Letter	16	58	3.87
Review	18	615	34.17
Total	**96**	**1,702**	

Note. ATC: Average total citations

Table 2. Top-10 prolific authors

	Author			Total	
Author	**Single**	**First**	**Other**	**TP**	**TC**
Yamakawa M	-	-	4	4	67
Lebbe C	-	-	3	3	131
Lorillon G	-	1	2	3	131
Mourah S	-	1	2	3	131
Tazi A	-	-	3	3	131
Chen YW	-	1	2	3	113
Gao CF	-	-	3	3	46
Li H	-	1	2	3	46
Wang CS	-	2	1	3	46
Takahashi T	-	1	2	3	35

Note. TP: Total publications & TC: Total citations

RESULTS

Annual Growth in LCS Research

Figure 3 illustrates the annual research productivity in LCS research. The first report on this topic was published in 1994. The second and third documents were published in 2002 and 2005, respectively. Although after 2005, research was published on the topic without any gap, slow growth in publications was observed with single-digit documents in all years except in 2013 when 10 documents were published. The year 2002 had highest number of citations (n=449), followed by 2014 and 2013, with 158 and 142 citations, respectively.

Document Types

The document types selected by the researchers are listed in **Table 1**. The document type "article" emerged as the most common document type used by the researchers in this area of study, followed by "review" and "letter". The same pattern was observed for citations secured against these document types. The document type "review" showed more impact (ATC=TC/TP), followed by "article" and "letter".

Most Prolific Authors

Table 2 presents top-10 most productive authors in LCS research. All top-10 authors contributed to single-digit publications. Only one contributed to four publications. Five authors contributed one publication, each as the first author. None of them contributed to the research as single authors. All top-authors have published collaborative research. Authors "Lebbe C", "Lorillon G", "Mourah S", and "Tazi A" received the highest number of citations.

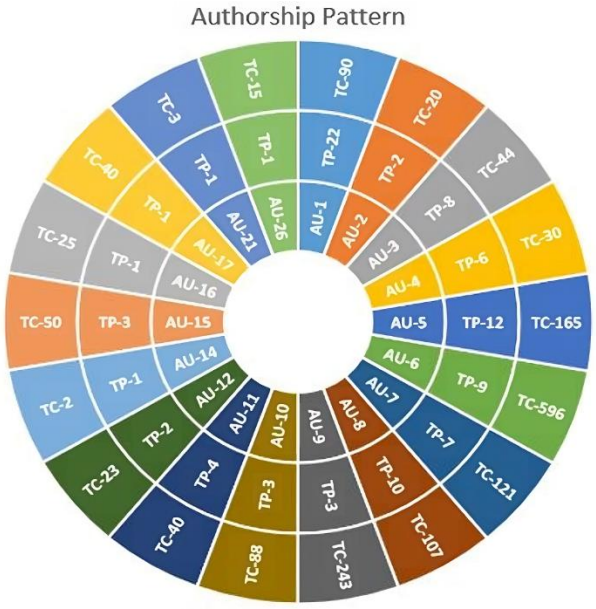


Figure 4. Authorship patterns in LCS research (Source: Authors' own elaboration, using MS Excel)

Authorship Patterns in LCS Research

Figure 4 depicts the authorship (AU) patterns in LCS research, which range from single-author to 26-author patterns. **Figure 4** discloses the trend of research by a single author, with the highest number of publications (n=22) contributed by researchers publishing research on the topic working in isolation. The five-author pattern contributed the second-highest number of publications (n=12), followed by the eight-author pattern. The citation-wise analysis ranked the six-author pattern at the top, followed by nine- and five-author patterns.

Most Productive Sources

Table 3 presents the sources of the publications preferred by the authors. "Journal of Cutaneous Pathology" secured the top position, with five publications. "International Journal of Hematology", "Diagnostic Pathology", and "Pathology International" jointly secured the second position. All documents published by "International Journal of Hematology" and "Diagnostic Pathology" received citations, but one document published by "Pathology International" did not receive any citations. The two publications in "Histopathology" had the highest number of citations, followed by the "International Journal of Hematology".

Most Cited Documents

Table 4 lists the most-cited documents. The document "Pileri SA, 2002, Histopathology" received the highest number of citations and also maintained the top position in terms of citations per year (CPY). The document "Go H, 2014, Histopathology" obtained the second-highest number of citations, followed by "Shao HP, 2011, Modern Pathol" and "Kairouz S, 2007, Am J Hematol".

Most Productive Organizations

Figure 5 shows most productive organizations publishing research on this topic. Japanese organizations emerged as the most productive and maintained five positions among top-10 productive organizations. Two organizations, each from the USA and France, maintained positions in the top-10 productive organizations. Only one organization from China appeared in the top-10 list. Kurume University, Japan, and the Mayo Clinic, USA, both secured the first position in terms of the number of publications. The organizations Inserm, France; Third (3rd) Military Medical University, China; and Yamagata University, Japan, secured a joint second position with four publications each.

Table 3. Top-10 sources of publications

Source	NCP	CP	TP	TC	ATC	JIF (2021)	Category rank by JIF
Journal of Cutaneous Pathology	0	5	5	53	10.6	1.458	Dermatology, 58/69 (Q4) & pathology 60/77 (Q4)
International Journal of Hematology	0	4	4	121	30.3	2.324	Hematology, 64/78 (Q4)
Diagnostic Pathology	0	4	4	50	12.5	3.196	Pathology, 39/77 (Q3)
Pathology International	1	3	4	6	1.5	2.121	Pathology, 53/77 (Q3)
American Journal of Dermatopathology	0	3	3	62	20.7	1.319	Dermatology, 60/69 (Q4)
Annals of Hematology	0	3	3	8	2.67	4.030	Hematology, 38/78 (Q2)
International Journal of Surgical Pathology	1	2	3	33	11.0	1.358	Pathology, 65/77 (Q4) & surgey, 174/213 (Q4)
Journal of Orthopaedic Science	1	2	3	27	9.0	1.805	Orthopedics, 60/86 (Q3)
Acta Haematologica	0	2	2	17	8.5	3.068	Hematology, 52/78 (Q2)
Histopathology	0	2	2	571	286.0	7.778	Cell biology, 49/195 (Q2) & pathology, 7/77 (Q1)

Note. NCP: Not cited paper; CP: Cited paper; TP: Total publications; TC: Total citations; ATC: Average total citations; & JIF: Journal impact factor

Table 4. Most cited documents

Paper	Title	TC	CPY
Pileri SA, 2002, Histopathology	Tumours of histiocytes and accessory dendritic cells: An immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases	449	22.45
Go H, 2014, Histopathology	Frequent detection of BRAF (V600E) mutations in histiocytic and dendritic cell neoplasms	122	15.25
Shao HP, 2011, Modern Pathol	Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: A study of seven cases	112	10.18
Kairouz S, 2007, Am J Hematol	Dendritic cell neoplasms: An overview	75	5.00
Lauritzen AF, 1994, Am J Clin Pathol	Histiocytic sarcomas and monoblastic leukemias–A clinical, histologic, and immunophenotypical study	61	2.18
West DS, 2013, Am J Surg Pathol	Clonally related follicular lymphomas and langerhans cell neoplasms expanding the spectrum of transdifferentiation	50	5.56
Kawase T, 2005, Int J Hematol	Cd56/Ncam-positive langerhans cell sarcoma: A clinicopathologic study of 4 cases	43	2.53
Lee JS, 2006, J Korean Med Sci	Langerhans cell sarcoma arising from langerhans cell histiocytosis: A case report	40	2.50
Ferringer T, 2006, Am J Dermatopath	Langerhans cell sarcoma	39	2.44

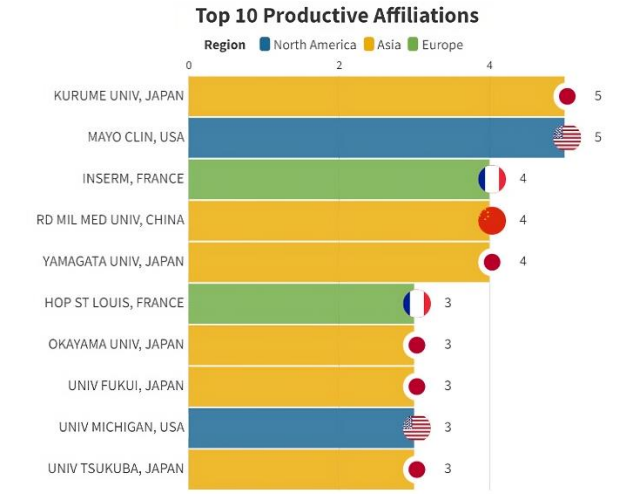


Figure 5. Most productive organizations in LCS research (Source: Authors' own elaboration, using https://flourish.studio)

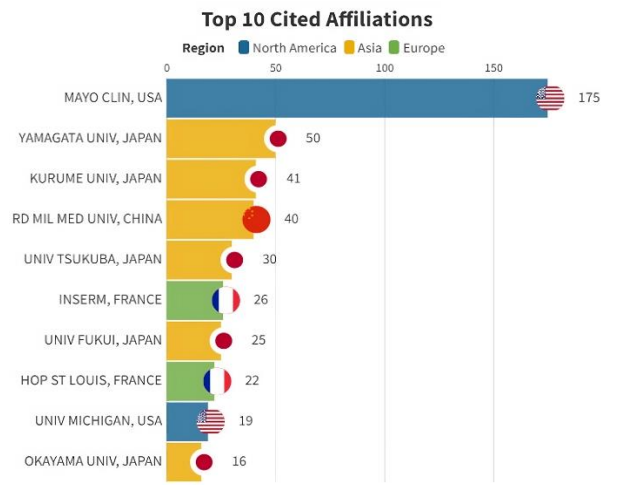


Figure 6. Top highly cited organizations in LCS research (Source: Authors' own elaboration, using https://flourish.studio)

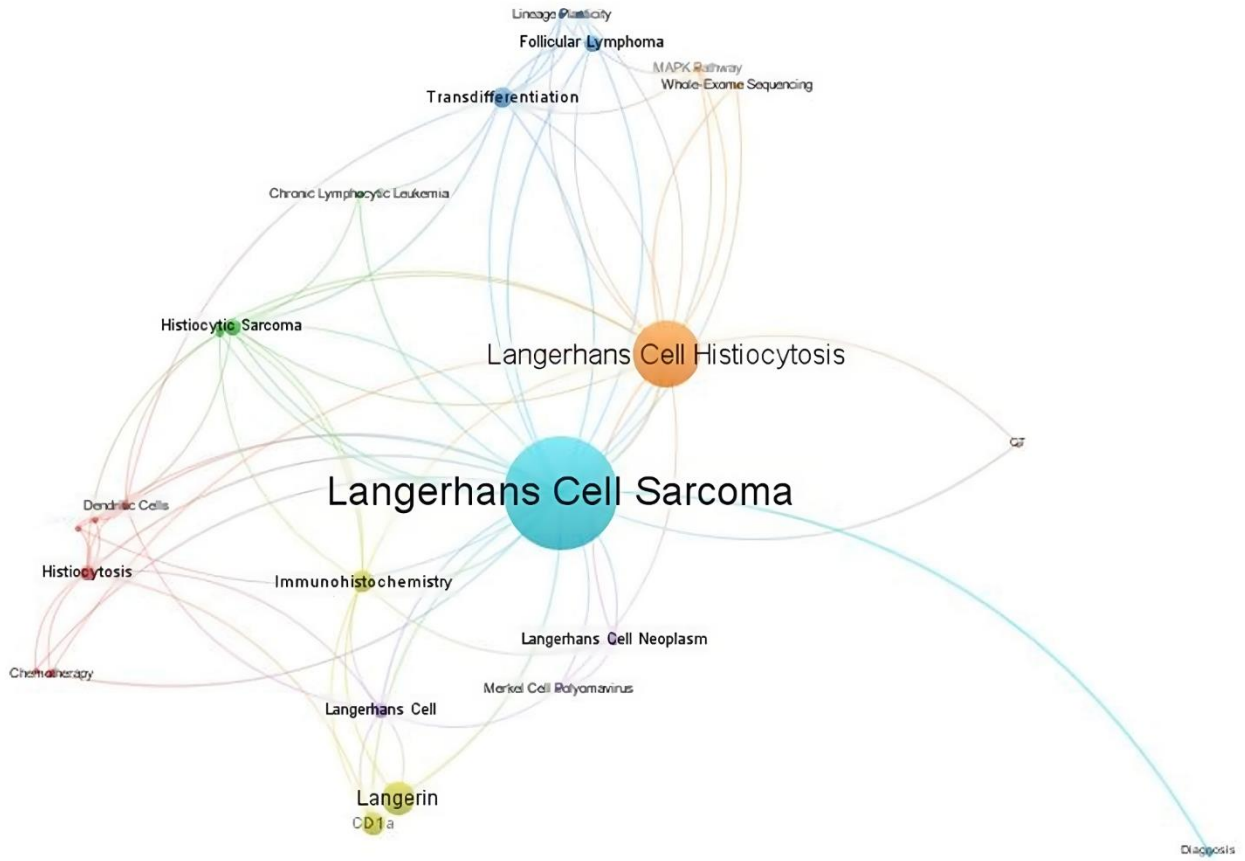


Figure 7. Most frequently used author keywords in LCS research (Source: Authors' own elaboration, using VOSviewer)

Top-10 Highly Cited Organizations

Figure 6 shows the top-10 cited organizations. The Mayo Clinic in the USA emerged as the leading organization with the highest number of citations, followed by Yamagata University and Kurume University in Japan. Okayama University, Japan, remains at the bottom of **Figure 6** with 16 citations.

Most Frequently Used Author Keywords in LCS Research

The most frequently used keywords are shown in **Figure 7**. Keywords with the same themes were gathered in one cluster and in the same color. The size of the circles reflects the frequency of keyword used by the researchers.

A large circle indicates a greater use of keywords. The most frequently used keywords were "langerhans cell sarcoma" and "langerhans cell histiocytosis".

Most Productive Countries

Figure 8 illustrates the country-wise productivity of research related to LCS. Japan contributed the highest number of publications (n=23), followed by the USA (n=22), and China (n=18). The citation analysis ranked the USA at the top, with 906

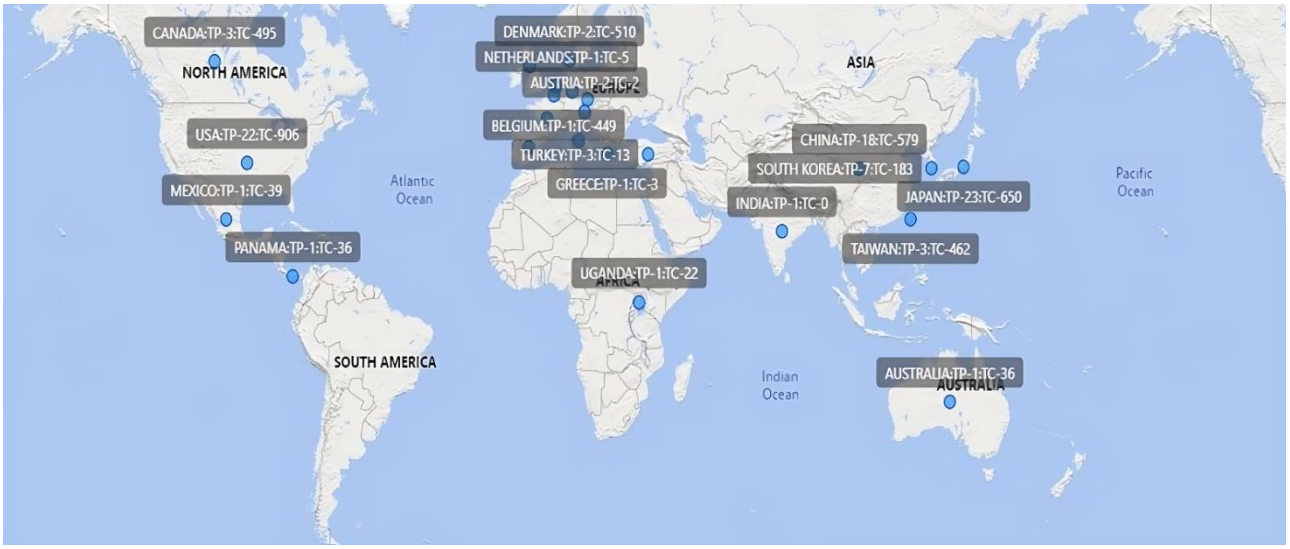
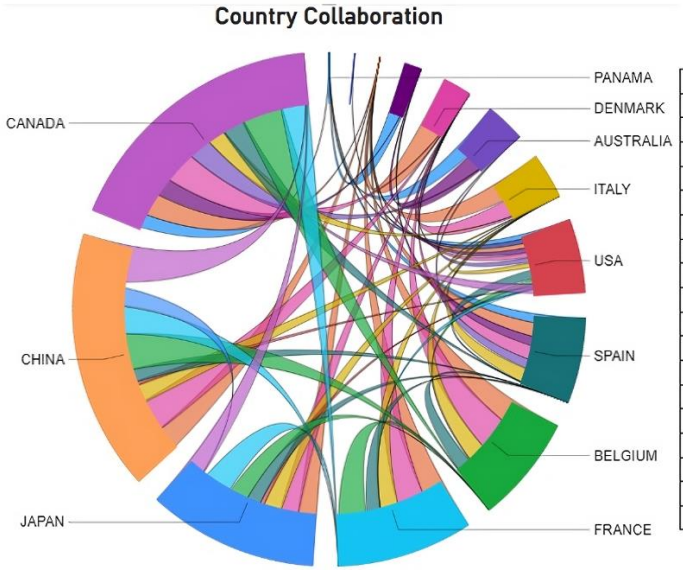


Figure 8. Highly productive countries in LCS research (Source: Authors' own elaboration, using Power BI)



From	To	TP
CANADA	BELGIUM	9
CHINA	BELGIUM	8
CHINA	CANADA	8
BELGIUM	DENMARK	7
CANADA	DENMARK	7
CHINA	DENMARK	7
CANADA	FRANCE	6
CHINA	FRANCE	6
FRANCE	BELGIUM	6
FRANCE	DENMARK	6
JAPAN	FRANCE	6
BELGIUM	GERMANY	5
CANADA	AUSTRALIA	5
CANADA	GERMANY	5
CANADA	SPAIN	5
CHINA	GERMANY	5
DENMARK	GERMANY	5
FRANCE	GERMANY	5

Figure 9. Most collaborative countries in LCS research (Source: Authors' own elaboration, using Power BI)

citations of 22 publications. Japan, the most productive country, stood second, with 650 citations, followed by China with 579 citations.

Highly Collaborative Countries

Figure 9 presents the highly collaborative countries researching the topic of LCS. Canada and China have emerged as the most collaborative countries, followed by Japan and France. Canada collaborated with Belgium, Denmark, France, Germany, Spain, and Australia. China has published papers in collaboration with Belgium, Canada, Denmark, and France.

DISCUSSION

This bibliometric analysis aimed to analyze the current research on LCS and discuss the trends in LCS, the current challenges that are being faced within clinical practice regarding diagnosis and management of the disease as well as highlight key authors and their studies that have had a great impact within LCS research. The efforts of these authors and their studies are crucial as they prove beneficial in identifying further potential areas of research. The current publications of LCS research are limited, and the annual scientific productivity has been slow, with minimal growth. A wide gap was observed between 1994 and 2002, with no published papers, and a gradual increase was observed from 2006 to 2015, with occasional falls in between. However, these results should not be interpreted as a lack of interest in LCS research, as the current data on LCS are limited owing to the rarity of its clinical presentation. A significant increase was observed in 2013, with 10 papers published in a single year. A total of 96 documents were included in our analysis consisting of articles, editorials, letters, and reviews, with their respective citations presented in **Table 1**.

One paper published in 2002 received the highest number of citations (n=449), followed by 158 citations of six papers in 2014, and 142 citations of 10 papers in 2010. An explanation for the high number of citations for a single paper could be the increased number of cases included within the paper, as well as the research itself focusing on a broader subject, such as histochemical staining and classification of not only LCS but

also of other diseases under the same lineage as LCS. Given that LCS is difficult to diagnose, papers explaining routine methods of diagnosis for this pathology have yielded greater citations and attention than publications in other subjects.

From our results, we can conclude that modern research on LCS is moving towards identifying the pathology through biochemical methods and tests within a clinical setting. The most common citation trend over the years is that papers published prior to 2015 tend to have higher citations than those published in recent years. This is understandable, as newer publications would have to rely on prior publications of the same lineage for references to literature and data. Another possible explanation is that articles began to be published in an electronic format in the early 2000s. This provided greater ease of access for researchers and facilitated an exponential growth in citations per year, as the authors were not restricted to obtaining hard copies of articles for referencing [26]. Despite the limited number (n=18), the published reviews were observed to have the greatest impact, followed by articles and letters. A possible explanation for this trend could be that reviews extensively cover a topic and all its respective areas and associations in comparison to articles and letters, which are more focused on a specific research question.

Among the top-10 prolific authors, none contributed solely to the publication and instead collaborated with other authors. **Figure 4** shows the authorship patterns regarding the number of papers published by a specific number of authors and their citations. This pattern reveals that authors working independently were capable of producing more publications; however, this trend was not the same for citations. Authors who collaborated published papers with a greater number of citations. “Journal of Cutaneous Pathology” was the preferred source of publication despite having an average citation count lower than “International Journal of Hematology”, which was the second most preferred source. However, the citation trends were not the same. Despite being ranked at the bottom with only two papers, the journal “Histopathology” claimed the top position for most citations. This data is promising as it shows that more articles are being published in high-impact journals and will help researchers choose suitable journals to submit manuscripts.

The Mayo Clinic in the USA secured the highest number of citations, followed by Yamagata University in Japan. Despite being second to the USA in terms of cited affiliations, Japan has contributed significantly towards LCS research, with five universities accumulating several citations. In terms of global productivity, Japan contributed extensively to LCS publications, with five universities emerging within the top-10 productive affiliations (**Figure 5**). Interestingly, universities were found to contribute more publications than hospital-based researchers. This could be due to rigorous publishing practices in the highly competitive environment observed within university institutions [27]. In addition, availability and time may have played a role in this trend, as universities can employ full-time researchers and have students working on research projects alongside their academics, compared to physicians within hospitals who have greater clinical responsibilities. However, it is important to note that this does not reflect the quality of the studies produced by individuals or organizations.

Another finding worth mentioning is that Asian organizations were seen to have been more productive than those in North America or Europe, despite being in the leading top-10 affiliations. This could be attributed to higher LCS prevalence within Asian populations, and a higher risk trend observed in certain geographical populations than in others. In the modern era, global collaboration for research is crucial, as it allows several organizations across the globe to pool resources and information to find breakthroughs and new discoveries. The global collaboration between countries in LCS research is shown in **Figure 9**. Developed countries were observed to collaborate more with other developed countries, with Canada and China leading in these areas as the countries with the most collaboration, especially in conjunction with European countries. There was little to no collaboration between developing and non-developed countries. This trend stresses the need for more global collaboration, especially among non-developed countries that lack the financial support to perform high-level research.

The core themes and subthemes of a study can be quickly identified using keywords. Word analysis reveals the ideas emphasized by a given study [23]. The network visualization map of co-occurring terms with an extraction frequency, depicted by the size of the clusters, is shown in **Figure 7**. Within our cluster analysis, the most used terms included “langerhans cell sarcoma” and “langerhans cell histiocytosis”. “Immunohistochemistry” was observed to have a cluster of its own (highlighted in green) with networks to “langerin” and “CD1A.” “Diagnosis” was seen to have a very low frequency only in direct relation to “langerhans cell sarcoma.” This pattern could be due to the lack of diagnostic clinical data for this disease. Hence, cluster analysis represents the research direction moving towards the diagnosis of LCS using immunohistochemistry.

The scarcity of literature regarding LCS has proved to be quite a challenge for researchers as well as clinicians, however, this has not stopped LCS research to discover more about this disease and recent progress has been fruitful. Regarding the origin sites of this disease, Howard et al. analyzed 66 cases of LCS and deducted that skin, lung, liver and lymph nodes were found to be the most common areas affected with the overall five-year survival being only 15% [28]. This study also revealed that patients with localized versions of this disease were seen to have a better outcome compared to those with multisystemic forms of LCS. It would be a preconceived statement to say that LCS is limited to only these few organ systems [28]. Interestingly, a rare phenomenon of LCS arising from the heart is also described [13, 14, 29]. Mohanty et al. described the uncommon presence of LCS features on fine needle aspiration cytology (FNAC) of the parotid gland [30].

Rare cases of the presence of LCS recurrence within the brain and the presence of LCS at the root of the tongue are described [31, 32]. From these recent studies we can identify that there is an increasingly growing trend towards reports on LCS derived from the head and neck region [33]. The article by Howard et al. sheds further light into these findings [28]. LCS may arise de-novo, but it also may arise spontaneously from LCH, which has been observed to be an uncommon presentation of this pathology. Prior studies have shown LCS arising from LCH [13, 34]. The mechanism of this particular etiology is unclear and is still a matter of debate. Studies conducted within the last decade have also revealed that the development of LCS may not only be restricted to the histiocyte lineage but may also arise from hematopoietic tumors such as hairy cell leukemia, chronic lymphocytic leukemia/small

lymphocytic lymphoma, and marginal-zone B-cell lymphoma [35-45].

An interesting disparity noticed amongst studies was the presence of BRAF within different studies of LCS. BRAFv600E mutations have been found positive within prior studies [46-50], which supports the hypothesis stated by prior studies that LCS patients may benefit from BRAF inhibitor therapy [46, 49, 51]. The efforts by Karai et al. have been beneficial in providing an insight that mutations within the TP53 gene can also be associated with LCS [52]. This finding was also further supported within the case report published by Kim et al., which also discussed on the presence of TP53 mutations in LCS as well as presenting us with a whole exonome analysis of LCS [12]. A further report published by Katsuragawa et al., also discussed about TP53 mutations and its presence within LCS; this report also discussed about CDKN2A deletion, which has rarely been seen within LCS [53]. This was a unique study because for the first time it discussed that the accumulation of damaged DNA by ultraviolet light could be a pre-disposing factor for the development of LCS. This study also further gave evidence that due to the overload of mutational burden and possible increased PD-1 expression within tumor cells therapy by immune-checkpoint inhibitors may provide benefit for the treatment of unresectable LCS [53]. Another intriguing study also supported the previously discussed theory of LCS arising from other hematopoietic tumors, however, this study also presented us with a new finding of the detection of KRAS p.G13D mutations on flourescence in situ hybridization analysis of LCS arising from follicular lymphoma. It could be hypothesized that close gene relations between the two tumors could provide an etiology for progression to LCS as well as possible mutation of KRAS p.G13D [54]. These findings may provide evidence that gene mutations and deletions specifically those related to the MARK pathway-related genes may contribute to development of LCS. However, these findings are not yet absolute due to the lack of literature currently present on LCS. From these recent studies we can conclude that whole exonome sequencing is a useful tool that not only identifies gene mutations but may also help us to understand the reason behind different morphological features and variations within LCS. More studies exploring the genetic mutations of LCS should be conducted, which could help in enhancing current literature and help in establishing new therapeutic strategies.

The diagnosis of LCS is challenging. Although the presence of Birbeck granules is characteristic for LCS, the case report by Lee et al. reported on the absence of Birbeck granules on ultrastructural examination in a patient diagnosed with LCS [13]. This unique anomaly could be due to an absence of langerin mutation, which has been linked to Birbeck granule formation [55]. Hence, from this finding we can conclude that the presence of Birbeck granules does not provide evidence for LCS and that accurate and improved methods of immunohistochemical staining must also be used in order to reach a definitive diagnosis for LCS. Another case report described additional findings of LCS with immunophentypical and morphological variability. Within this study the author described a case of LCS that presented with variable chronic inflammatory infiltrate alongside the common findings of atypical cells, abundant nuclei and bizarre nuclei alongside this it was also unique to note that this specific form of LCS was also positive for CD45, which is an uncommon finding. Immunohistochemistry has shown to be crucial in identifying LCS and is currently listed as one of the necessary investigations to diagnose LCS. Studies have shown that LCS is not only exclusive to the commonly tested stains such as S-100, CD68 and CD1a. A new finding was presented by Ferringer et al., who revealed the presence of the aberrant CD31 expression [4]. Also, interesting to note was that this specific case presented with an absence of CD68, which is usually a common presentation in most cases for LCS. A recent experiment introduced a new possible diagnostic option, which involved the use of liquid cytology combined with immunohistochemistry to provide a more definitive diagnosis for LCS. The results of this experiment were promising and showed a more efficient presentation of affected cells with a clearer background [56]. This technique could prove valuable in differentiating between neoplasms; however, this statement is yet to be supported by further studies involving liquid-based cytology.

Current treatment involving LCS has been observed to be expanding from the chemotherapy combined with drug therapy, anthracyclines, platinum based regimes to surgical resection [28, 42, 57, 58]. A recent study by Zanwar et al. involved the use of immune inhibitor drugs therapy for multisystem LCS [59]. The results of this study yielded positive findings in remission of LCS [59]. The results of this study highlight potential research into the use of immune checkpoint inhibitors such as pembrolizumab. Another unique case described the results of pegylated interferon-alpha2b for control of cutaneous LCS [60]. The positive results of this study provide a unique insight into the fact that despite aggressive atypica and proliferation the affected cells may still retain properties of dendritic cells. With regard to cutaneous forms of LCS, treatment with pegylated interferon-alpha2b may prove beneficial in remission and long-term therapy for affected individuals. In summary, key hotspots for potential areas of research for management of LCS include the need for further studies highlighting the use of combination therapies involving immune checkpoint inhibitors and chemotherapy. This regime could prove beneficial for the management of LCS.

To the best of our knowledge, this is the first bibliometric analysis conducted on LCS that provides a robust summary of the direction of its research and potential hotspots to be explored. Despite these promising results, this bibliometric analysis is not without limitations. The primary limitation of this study is the lack of literature that provides a more extensive analysis. Because we only used the WoS to extract publications, there may be a degree of selection bias as majority of the articles that are present within the WoS database are in English. Articles present in other languages such as Russian and Chinese may have been unintentionally excluded from within our analysis. Furthermore, keyword heterogeneity may have slightly influenced our cluster analysis.

CONCLUSIONS

This study statistically analyzed and summarized the distribution of LCS publications and identified potential future areas of exploration in LCS research. The current literature on LCS is minimal, emphasizing the need for more publications, especially within areas regarding the diagnosis and histochemical staining with CD markers for this pathology. Whole exonome genome sequencing in recent studies has

shown to be an effective tool in recognizing genetic mutations. Future studies and case reports should be encouraged to apply this useful technique as it may help in establishing a better understanding of this disease and help in its management.

With regard to the treatment, immune checkpoint inhibitors have been shown to have promising potential in treating LCS. Leading countries within this field of research include Japan and the US, with extensive global collaboration between Canada, China, and European countries. These results will be useful in guiding future research entities and collaborations.

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